Open Forum Infectious Diseases

MAJOR ARTICLE

Prevalence and Predictors of Concomitant Bacterial Infections in Patients With Respiratory Viruses in Ontario: A Cohort Study

Yue Wang,[1,2] Sarah Swayze,[1] Kevin A. Brown,[1,3,4] Derek R. MacFadden,[1,5] Samantha M. Lee,[1] Kevin L. Schwartz,[1,3,4,6] Nick Daneman,[1,3,7] and Bradley J. Langford[3,4,8]

[1]ICES, Toronto, Ontario, Canada, [2]Department of Biology, McMaster University, Hamilton, Ontario, Canada, [3]Public Health Ontario, Toronto, Ontario, Canada, [4]Dalla Lana School of Public Health, Toronto, Ontario, Canada, [5]The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, [6]Unity Health Toronto, Toronto, Ontario, Canada, [7]Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada, and [8]Hotel Dieu Shaver Health and Rehabilitation Center, St. Catharines, Ontario, Canada

Background. To investigate the prevalence of concomitant bacterial infection across common viral infections.

Methods. This population-based cohort study included patients infected with influenza A and B (FLUA, FLUB) and respiratory syncytial virus (RSV) in Ontario between 2017 and 2019 and patients with SARS-CoV-2 between 2020 and 2021. Specific bacteria present in concomitant infections were identified. Concomitant infections were further classified into different categories (eg, coinfection −2 to +2 days from viral infection and secondary infection >2 days after viral infection). We used logistic regression models to estimate the odds of bacterial infections for FLUA, FLUB, and RSV relative to SARS-CoV-2 while adjusting for confounders.

Results. A total of 4230 (0.5%, 885 004) viral cases had concomitant bacterial infections, encompassing 422 of FLUB (4.7%, 8891), 861 of FLUA (3.9%, 22 313), 428 of RSV (3.4%, 12 774), and 2519 of COVID-19 (0.3%, 841 026). The most prevalent species causing concomitant bacterial infection were *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa*. When compared with SARS-CoV-2, the adjusted odds ratio for bacterial infection was 1.69 (95% CI, 1.48–1.93) for FLUA, 2.30 (95% CI, 1.97–2.69) for FLUB, and 1.56 (95% CI, 1.33–1.82) for RSV. The adjusted odds of coinfection in patients with SARS-CoV-2 were lower but higher for secondary infection as compared with the other viruses.

Conclusions. A higher prevalence and risk of concomitant bacterial infection were found in FLUA, FLUB, and RSV as compared with SARS-CoV-2, although this is largely driven by coinfections. Ongoing surveillance efforts are needed to compare the risk of concomitant infections during periods when these viruses are cocirculating.

Keywords. concomitant bacterial infections; COVID-19; influenza; respiratory syncytial virus; respiratory viral infections.

Concomitant infections in patients with viral respiratory tract infections can increase the risk of patient morbidity and mortality [1]. Respiratory viruses such as influenza A (FLUA), influenza B (FLUB), respiratory syncytial virus (RSV), and SARS-CoV-2 [2, 3] can contribute to an increased risk of concomitant bacterial infections through a variety of mechanisms, including dysregulation of the immune response, airway epithelial damage, and hand-nose contact [4–7].

Previous studies have evaluated the risk of coinfections and secondary infections in patients with COVID-19 [8–10]. Although the overall prevalence of bacterial infections with COVID-19 is low, a higher prevalence of secondary infection has been observed for patients who are critically ill [11–13]. A systematic review and meta-analysis of 148 studies between December 2019 and May 2021, including 362 976 patients with COVID-19, revealed a 5.3% rate of bacterial coinfection and a 18.4% rate of secondary infection [12]. A more recent study analyzing 194 660 COVID-19 admissions in Victoria, Australia, from 2020 to 2023 noted a 6.9% rate of secondary infections, with prevalence varying across different COVID-19 waves [14]. Regarding influenza and RSV, the prevalence of concomitant bacterial infections has been reported to be as high as 30% [15, 16].

However, there is a lack of direct comparative data between various viral infections and their risk of concomitant infection. Comparison across studies is hindered by differential testing rates, laboratory practices, and patient populations. In this population-based study across all health care settings, we aimed

Received 27 August 2024; editorial decision 21 November 2024; accepted 29 November 2024; published online 3 December 2024

Correspondence: Dr. Yue Wang, Department of Biology, McMaster University, 1280 Main St West, Hamilton, Ontario, Canada L8S 4L8 (wangy660@mcmaster.ca).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofae701

to describe the prevalence of microbiologically confirmed concomitant infections in patients with laboratory-confirmed SARS-CoV-2, FLUA, FLUB, and RSV. We also aimed to determine if risk factors, such as patient characteristics, are associated with differential risks of concomitant bacterial infection.

METHODS

Study Design

The retrospective cohort study evaluated individuals with any positive molecular test results for at least 1 of SARS-CoV-2, FLUA, FLUB, or RSV between 1 January 2017 and 31 December 2021, in Ontario, Canada. Data for SARS-CoV-2 spanned 2020 to 2021, while data for FLUA, FLUB, and RSV covered 2017 to 2019.

Data Sources

Data sets in this study included Ontario Laboratories Information System (OLIS), OLIS COVID-19 Laboratory Data, COVID19 Integrated Testing, Case and Contact Management System, among others (Supplementary Table 1). These data sets were linked by unique encoded identifiers and analyzed at ICES. ICES is an independent nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for the purpose of evaluating and improving the health system.

Study Cohort

The index event was a positive molecular test result for any of the following viral respiratory infections based on the date of test collection: SARS-CoV-2, FLUA, FLUB, and RSV. Individuals were excluded if they were not registered for Ontario health care services at the index date or had missing information, such as age, sex, birth date, or postal code. Meanwhile, individuals were also excluded if they had positive molecular test results with the same virus in the 28 days prior to the index viral infection [17]. Viral cases were not considered positive outcomes if patients had fungal infections, mixed growth of bacterial organisms, subsequent cultures of the same organisms, or organisms that are potential contaminants: coagulase-negative staphylococci, *Bacillus*, *Micrococcus*, *Corynebacterium*, *Paenibacillus*, *Lactobacillus*, and *Propionibacterium* (recently reclassified as *Cutibacterium*). Figure 1 depicts the cohort selection process.

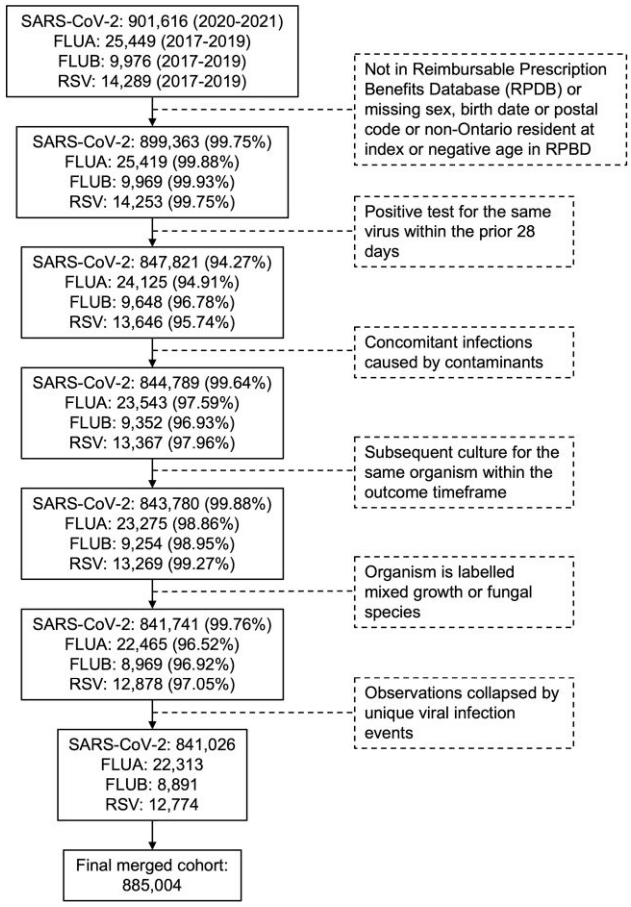

Figure 1. The cohort selection process shows the number of viral cases with any of the 4 respiratory viral infections recorded during the examination window and exclusion criteria. Percentages represent those remaining from the previous step. The final data sets included observations for each unique viral infection event. Abbreviations: FLUA, influenza A; FLUB, influenza B; RSV, respiratory syncytial virus.

Covariates

The primary predictor variable in this study was the specific virus causing respiratory infection: SARS-CoV-2, FLUA, FLUB, or RSV. SARS-CoV-2 served as the reference category against which the effects of the other viruses on patient outcomes were assessed and compared.

Other potential predictors were as follows: individual-level demographic characteristics at the time of viral test (age, sex, geographic region), year of viral test, setting at the time of viral test (community, hospital ward, intensive care unit [ICU], long term care), vaccination status (influenza, COVID-19, pneumococcal diseases), health care use in the prior year (number of physician visits, days spent in ICU and hospital ward), individual medical conditions (congestive heart failure, asthma, dementia, diabetes, acute myocardial infarction, cardiac arrhythmia, cancers, chronic obstructive pulmonary disease, coronary syndrome [excluding acute myocardial infarction], hypertension, mood disorders [including mood, anxiety, depression, and other nonpsychotic disorders], other mental illnesses, stroke, osteoarthritis, osteoporosis, rheumatoid arthritis, and renal failure), multimorbidity level [18], and immunosuppression.

Outcomes

The primary outcome was the presence or absence of concomitant bacterial infections in blood and respiratory specimens around the time of the viral test (−2 to +14 days of index viral infection). Respiratory specimens were categorized as follows:

Table 1. Baseline Characteristics of Individuals With Viral Infections

Characteristic	Any Viral Infection (n = 885 004)	SARS-CoV-2 (n = 841 026)	FLUA (n = 22 313)	FLUB (n = 8891)	RSV (n = 12 774)
Sex					
Female	449 195 (50.8)	426 153 (50.7)	11 831 (53.0)	4754 (53.5)	6457 (50.5)
Male	435 809 (49.2)	414 873 (49.3)	10 482 (47.0)	4137 (46.5)	6317 (49.5)
Age, y					
0–17	142 947 (16.2)	128 615 (15.3)	5142 (23.0)	1758 (19.8)	7432 (58.2)
18–64	632 305 (71.4)	621 821 (73.9)	6327 (28.4)	2784 (31.3)	1373 (10.7)
≥65	109 752 (12.4)	90 590 (10.8)	10 844 (48.6)	4349 (48.9)	3969 (31.1)
Year of viral test					
2017	12 337 (1.4)	0 (0.0)	6215 (27.9)	2010 (22.6)	4112 (32.2)
2018	16 977 (1.9)	0 (0.0)	7636 (34.2)	5365 (60.3)	3976 (31.1)
2019	14 664 (1.7)	0 (0.0)	8462 (37.9)	1516 (17.1)	4686 (36.7)
2020	192 357 (21.7)	192 357 (22.9)	0 (0.0)	0 (0.0)	0 (0.0)
2021	648 669 (73.3)	648 669 (77.1)	0 (0.0)	0 (0.0)	0 (0.0)
Setting at index date					
Community	824 992 (93.2)	807 843 (96.1)	8955 (40.1)	3618 (40.7)	4576 (35.8)
Hospital	42 217 (4.8)	19 407 (2.3)	11 243 (50.4)	4438 (49.9)	7129 (55.8)
Intensive care unit	4852 (0.5)	2461 (0.3)	1202 (5.4)	459 (5.2)	730 (5.7)
Long-term care	12 943 (1.5)	11 315 (1.3)	913 (4.1)	376 (4.2)	339 (2.7)
Vaccination status					
Influenza: last 6 mo	99 576 (11.3)	91 805 (10.9)	3955 (17.7)	1826 (20.5)	1990 (15.6)
Pneumococcal: last 5 y	43 355 (4.9)	38 689 (4.6)	1293 (5.8)	384 (4.3)	2989 (23.4)
COVID-19: 1 dose	46 936 (5.3)	46 936 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19: 2 doses	208 817 (23.6)	208 817 (24.8)	0 (0.0)	0 (0.0)	0 (0.0)
Health care utilization, mean ± SD					
Days spent in hospital: previous 365 d	0.84 ± 7.20	0.62 ± 6.07	5.07 ± 18.10	5.27 ± 18.09	5.36 ± 17.35
Days spent in ICU: previous 365 d	0.11 ± 2.40	0.07 ± 1.69	0.70 ± 8.64	0.62 ± 5.35	1.20 ± 7.62
No. of physician visits: last 12 mo	5.49 ± 7.40	5.34 ± 7.27	8.02 ± 9.29	9.13 ± 9.77	8.05 ± 8.72
Comorbidity level: medical conditions[a]					
0 or 1	517 227 (58.4)	500 884 (59.6)	6579 (29.5)	2427 (27.3)	7337 (57.4)
2	138 466 (15.6)	135 095 (16.1)	1954 (8.8)	829 (9.3)	588 (4.6)
3	88 273 (10.0)	84 950 (10.1)	1959 (8.8)	863 (9.7)	501 (3.9)
4	53 215 (6.0)	49 724 (5.9)	2035 (9.1)	818 (9.2)	638 (5.0)
≥5	87 823 (9.9)	70 373 (8.4)	9786 (43.9)	3954 (44.5)	3710 (29.0)
Immunocompromised	27 928 (3.2)	22 995 (2.7)	2497 (11.2)	1208 (13.6)	1228 (9.6)
Medical condition					
COPD	18 113 (2.0)	11 604 (1.4)	3483 (15.6)	1446 (16.3)	1580 (12.4)
Hypertension	160 687 (18.2)	140 698 (16.7)	11 346 (50.8)	4584 (51.6)	4059 (31.8)
Dementia	24 937 (2.8)	18 882 (2.2)	3428 (15.4)	1403 (15.8)	1224 (9.6)
Diabetes	93 806 (10.6)	82 900 (9.9)	6277 (28.1)	2496 (28.1)	2133 (16.7)
Asthma	145 730 (16.5)	135 662 (16.1)	5214 (23.4)	2126 (23.9)	2728 (21.4)
Cancer	191 054 (21.6)	174 600 (20.8)	9162 (41.1)	3879 (43.6)	3413 (26.7)
Stroke	14 306 (1.6)	10 950 (1.3)	1948 (8.7)	724 (8.1)	684 (5.4)
Renal failure	25 717 (2.9)	18 574 (2.2)	3862 (17.3)	1678 (18.9)	1603 (12.5)
Nonpsychotic disorders[b]	284 618 (32.2)	266 665 (31.7)	10 389 (46.6)	4258 (47.9)	3306 (25.9)
Other mental illnesses	168 805 (19.1)	156 421 (18.6)	6965 (31.2)	2797 (31.5)	2622 (20.5)
Rheumatoid arthritis	7335 (0.8)	6202 (0.7)	624 (2.8)	270 (3.0)	239 (1.9)
Osteoarthritis	255 709 (28.9)	235 811 (28.0)	11 297 (50.6)	4695 (52.8)	3906 (30.6)
Osteoporosis	20 782 (2.3)	17 111 (2.0)	1988 (8.9)	907 (10.2)	776 (6.1)
Cardiac arrhythmia	32 554 (3.7)	26 325 (3.1)	3421 (15.3)	1406 (15.8)	1402 (11.0)
Acute myocardial infarction	9936 (1.1)	7510 (0.9)	1392 (6.2)	519 (5.8)	515 (4.0)
Congestive heart failure	21 654 (2.4)	14 231 (1.7)	3991 (17.9)	1596 (18.0)	1836 (14.4)
Coronary syndrome	44 681 (5.0)	35 470 (4.2)	5259 (23.6)	2049 (23.0)	1903 (14.9)
Local health integration network					
Erie St Clair	39 547 (4.5)	38 192 (4.5)	631 (2.8)	293 (3.3)	431 (3.4)
South West	42 355 (4.8)	38 054 (4.5)	2080 (9.3)	765 (8.6)	1456 (11.4)
Waterloo Wellington	42 829 (4.8)	41 120 (4.9)	841 (3.8)	467 (5.3)	401 (3.1)

Table 1. Continued

Characteristic	Any Viral Infection (n = 885 004)	SARS-CoV-2 (n = 841 026)	FLUA (n = 22 313)	FLUB (n = 8891)	RSV (n = 12 774)
Hamilton Niagara Haldimand Brant	88 308 (10.0)	83 035 (9.9)	2453 (11.0)	866 (9.7)	1954 (15.3)
Central West	113 269 (12.8)	108 327 (12.9)	2503 (11.2)	876 (9.9)	1563 (12.2)
Mississauga Halton	88 677 (10.0)	84 593 (10.1)	2118 (9.5)	748 (8.4)	1218 (9.5)
Toronto Central	93 697 (10.6)	88 905 (10.6)	2343 (10.5)	1504 (16.9)	945 (7.4)
Central West	150 433 (17.0)	145 238 (17.3)	2878 (12.9)	991 (11.1)	1326 (10.4)
Central East	104 768 (11.8)	100 400 (11.9)	2347 (10.5)	865 (9.7)	1156 (9.0)
South East	13 887 (1.6)	12 933 (1.5)	454 (2.0)	128 (1.4)	372 (2.9)
Champlain	61 618 (7.0)	59 452 (7.1)	1210 (5.4)	510 (5.7)	446 (3.5)
North Simcoe Muskoka	22 684 (2.6)	19 875 (2.4)	1411 (6.3)	504 (5.7)	894 (7.0)
North East	15 713 (1.8)	14 325 (1.7)	767 (3.4)	274 (3.1)	347 (2.7)
North West	7219 (0.8)	6577 (0.8)	277 (1.2)	100 (1.1)	265 (2.1)

Data are presented as No. (%) unless noted otherwise.

Abbreviations: COPD, chronic obstructive pulmonary disease; FLUA, influenza A; FLUB, influenza B; ICU, intensive care unit; RSV, respiratory syncytial virus.

[a]From medical conditions listed below.

[b]Mood, anxiety, depression, and others.

bronchoalveolar lavage and endotracheal aspirate as *lower respiratory*, sputum as *upper respiratory*, and samples without specific information as *respiratory–not specified*.

Two secondary outcomes were established per the time of bacterial presentation in relation to viral detection: coinfection and secondary infection. Bacterial infections were defined as coinfection if organisms were identified from −2 to +2 days after viral detection and secondary infection if identified after 2 days and up to 14 days from viral detection.

Statistical Analysis

We utilized univariate and multivariable logistic regression to examine the association between respiratory viruses and concurrent bacterial infections, comparing FLUA, FLUB, and RSV against the reference SARS-CoV-2. In the multivariable models, the year of the viral test, with all baseline demographic and clinical characteristic data listed in the Covariates section, was included to adjust for any potential confounding effect on the relationship between respiratory viruses and bacterial infections. Likewise, the analyses were repeated for coinfection and secondary infection. A stratified analysis by setting (eg, community, hospital [non-ICU], hospital ICU, and long-term care) at the index date was conducted for concomitant bacterial infection, coinfection, and secondary infection to explore potential differences in patient severity and variations in testing rates.

Several subgroup analyses were performed. In 1 of these analyses, we assessed how concomitant infections varied across waves of COVID-19. The COVID-19 cases were grouped into 3 waves based on the date of infection: the wild type wave (date of viral testing: 1 March 2020–31 March 2021), the alpha wave (1 April 2021–31 June 2021), and the delta wave (1 July 2021–31 December 2021) [19]. In addition, we grouped concomitant bacterial infections into blood and respiratory based on the specimen source. To delineate the potential impact of pandemic-related infection prevention measures, we evaluated the relative risks for each of the top 3 most common species: *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa*.

All analyses were conducted with SAS Enterprise Guide version 8.3, and results were visualized by R version 4.3.1.

RESULTS

We observed 885 004 respiratory viral infections among 864 422 unique patients during the 5-year study period (Table 1). From 2017 to 2019, there were 22 313 FLUA cases among 22 221 patients, 8891 FLUB cases among 8854 patients, and 12 774 RSV cases among 12 648 patients. Between 2020 and 2021, 841 026 SARS-CoV-2 cases among 825 851 patients. Approximately half of viral infections were among females (n = 449 195, 50.8%), which was similar across the different viral infections. Patients with SARS-CoV-2 tended to be younger than those with FLUA, FLUB, and RSV (10.8%, 48.6%, 48.9%, and 31.1% were aged ≤65 years, respectively). Most cases of SARS-CoV-2 were identified in the community (96.1%) as compared with FLUA, FLUB, and RSV, where the majority were identified in hospitals (50.4%, 49.9%, and 55.8%). Patients of FLUA/B and RSV experienced more frequent exposure to health care facilities and were prone to higher comorbidity level, immunosuppression, and more medical conditions.

Overall, 4230 (0.48%) of the 885 004 viral infection cases were associated with concomitant bacterial infection (Table 2). Concomitant infection in patients with SARS-CoV-2 (2519/841 026, 0.3%) was less common than in patients with FLUA (861/22,313, 3.9%), FLUB (422/8891, 4.7%), and RSV (428/12 774, 3.4%). Patients with concomitant SARS-CoV-2 and bacterial infections were more likely to be male (1516/251 960.2%) as compared with those with FLUA (447/861, 51.9%), FLUB

Table 2. Cases per Infection Group by Virus and Baseline Characteristics of Individuals With Concomitant Bacterial Infections

Characteristic	Any Viral Infection (n = 4230)	SARS-CoV-2 (n = 2519)	FLUA (n = 861)	FLUB (n = 422)	RSV (n = 428)
Infection group					
Coinfection	2338 (55.3)	988 (39.2)	672 (78.0)	334 (79.1)	344 (80.4)
Secondary infection	1979 (46.8)	1584 (62.9)	205 (23.8)	96 (22.7)	94 (22.0)
Blood infection	1779 (42.1)	1145 (45.5)	296 (34.4)	156 (37.0)	182 (42.5)
Respiratory infection	2610 (61.7)	1503 (59.7)	582 (67.6)	273 (64.7)	252 (58.9)
Staphylococcus aureus	1177 (27.8)	772 (30.6)	213 (24.7)	124 (29.4)	68 (15.9)
Pseudomonas aeruginosa	462 (10.9)	267 (10.6)	104 (12.1)	41 (9.7)	50 (11.7)
Streptococcus pyogenes	546 (12.9)	398 (15.8)	80 (9.3)	33 (7.8)	35 (8.2)
Sex					
Female	1838 (43.5)	1003 (39.8)	414 (48.1)	212 (50.2)	209 (48.8)
Male	2392 (56.5)	1516 (60.2)	447 (51.9)	210 (49.8)	219 (51.2)
Age, y					
0–17	512 (12.1)	105 (4.2)	187 (21.7)	74 (17.5)	146 (34.1)
18–64	1870 (44.2)	1333 (52.9)	297 (34.5)	145 (34.4)	95 (22.2)
≥65	1848 (43.7)	1081 (42.9)	377 (43.8)	203 (48.1)	187 (43.7)
Year of viral test					
2017	487 (11.5)	0 (0.0)	246 (28.6)	98 (23.2)	143 (33.4)
2018	668 (15.8)	0 (0.0)	275 (31.9)	258 (61.1)	135 (31.5)
2019	556 (13.1)	0 (0.0)	340 (39.5)	66 (15.6)	150 (35.0)
2020	780 (18.4)	780 (31.0)	0 (0.0)	0 (0.0)	0 (0.0)
2021	1739 (41.1)	1739 (69.0)	0 (0.0)	0 (0.0)	0 (0.0)
Setting at index date					
Community	1469 (34.7)	1082 (43.0)	210 (24.4)	84 (19.9)	93 (21.7)
Hospital	1701 (40.2)	792 (31.4)	437 (50.8)	235 (55.7)	237 (55.4)
Intensive care unit	1005 (23.8)	596 (23.7)	209–213	103 (24.4)	93–97
Long-term care	55 (1.3)	49 (1.9)	1–5	0 (0.0)	1–5
Vaccination status					
Influenza vaccinated: last 6 mo	712 (16.8)	389 (15.4)	140 (16.3)	105 (24.9)	78 (18.2)
Pneumococcal vaccinated: last 5 y	261 (6.2)	164 (6.5)	34 (3.9)	13 (3.1)	50 (11.7)
COVID-19: 1 dose	197 (4.7)	197 (7.8)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19: 2 doses	144 (3.4)	144 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)
Health care utilization, mean ± SD					
Days spent in hospital: previous 365 d	6.85 ± 19.93	6.20 ± 17.58	7.73 ± 26.22	6.34 ± 16.63	9.43 ± 21.02
Days spent in ICU: previous 365 d	4.06 ± 21.66	4.58 ± 18.14	3.97 ± 34.78	1.77 ± 6.97	3.50 ± 14.57
No. of physician visits: last 12 mo	10.33 ± 11.09	10.56 ± 11.30	10.01 ± 11.22	9.82 ± 10.23	10.11 ± 10.42
Comorbidity level: medical conditions[a]					
0 or 1	1128 (26.7)	657 (26.1)	220 (25.6)	96 (22.7)	155 (36.2)
2	474 (11.2)	344 (13.7)	73 (8.5)	28 (6.6)	29 (6.8)
3	500 (11.8)	360 (14.3)	72 (8.4)	40 (9.5)	28 (6.5)
4	454 (10.7)	293 (11.6)	90 (10.5)	38 (9.0)	33 (7.7)
≥5	1674 (39.6)	865 (34.3)	406 (47.2)	220 (52.1)	183 (42.8)
Immunocompromised	557 (13.2)	243 (9.6)	156 (18.1)	73 (17.3)	85 (19.9)
Medical conditions					
COPD	571 (13.5)	190 (7.5)	194 (22.5)	106 (25.1)	81 (18.9)
Hypertension	2184 (51.6)	1303 (51.7)	444 (51.6)	235 (55.7)	202 (47.2)
Dementia	316 (7.5)	152 (6.0)	76 (8.8)	54 (12.8)	34 (7.9)
Diabetes	1472 (34.8)	947 (37.6)	266 (30.9)	142 (33.6)	117 (27.3)
Asthma	986 (23.3)	466 (18.5)	264 (30.7)	131 (31.0)	125 (29.2)
Cancer	1501 (35.5)	806 (32.0)	344 (40.0)	187 (44.3)	164 (38.3)
Stroke	263 (6.2)	158 (6.3)	58 (6.7)	24 (5.7)	23 (5.4)
Renal failure	806 (19.1)	383 (15.2)	207 (24.0)	119 (28.2)	97 (22.7)
Nonpsychotic disorders[b]	1970 (46.6)	1162 (46.1)	433 (50.3)	217 (51.4)	158 (36.9)
Other mental illnesses	1446 (34.2)	807 (32.0)	334 (38.8)	169 (40.0)	136 (31.8)
Rheumatoid arthritis	127 (3.0)	58 (2.3)	34 (3.9)	15 (3.6)	20 (4.7)
Osteoarthritis	2258 (53.4)	1364 (54.1)	460 (53.4)	239 (56.6)	195 (45.6)
Osteoporosis	271 (6.4)	133 (5.3)	73 (8.5)	42 (10.0)	23 (5.4)

Table 2. Continued

Characteristic	Any Viral Infection (n = 4230)	SARS-CoV-2 (n = 2519)	FLUA (n = 861)	FLUB (n = 422)	RSV (n = 428)
Cardiac arrhythmia	499 (11.8)	244 (9.7)	122 (14.2)	70 (16.6)	63 (14.7)
Acute myocardial infarction	229 (5.4)	123 (4.9)	47 (5.5)	30 (7.1)	29 (6.8)
Congestive heart failure	654 (15.5)	285 (11.3)	184 (21.4)	94 (22.3)	91 (21.3)
Coronary syndrome	894 (21.1)	471 (18.7)	210 (24.4)	106 (25.1)	107 (25.0)
Local health integration network					
Erie St Clair or South West	288 (6.8)	129 (5.1)	67 (7.8)	37 (8.8)	55 (12.9)
Waterloo Wellington	116 (2.7)	57 (2.3)	28 (3.3)	24 (5.7)	7 (1.6)
Hamilton Niagara Haldimand Brant	371 (8.8)	249 (9.9)	53 (6.2)	23 (5.5)	46 (10.7)
Central West	1069 (25.3)	636 (25.2)	238 (27.6)	95 (22.5)	100 (23.4)
Mississauga Halton	365 (8.6)	224 (8.9)	77 (8.9)	26 (6.2)	38 (8.9)
Toronto Central	464 (11.0)	266 (10.6)	84 (9.8)	65 (15.4)	49 (11.4)
Central West	628 (14.8)	449 (17.8)	89 (10.3)	47 (11.1)	43 (10.0)
Central East	429 (10.1)	272 (10.8)	86 (10.0)	39 (9.2)	32 (7.5)
South East or Champlain	249 (5.9)	109 (4.3)	68 (7.9)	41 (9.7)	31 (7.2)
North Simcoe Muskoka	93 (2.2)	44 (1.7)	27 (3.1)	10 (2.4)	12 (2.8)
North East or North West	158 (3.7)	84 (3.3)	44 (5.1)	15 (3.6)	15(3.5)

To comply with ICES privacy and confidentiality safeguards, values for several local health integration networks were aggregated.

Abbreviations: COPD, chronic obstructive pulmonary disease; FLUA, influenza A; FLUB, influenza B; ICU, intensive care unit; RSV, respiratory syncytial virus.

[a]From medical conditions listed below.

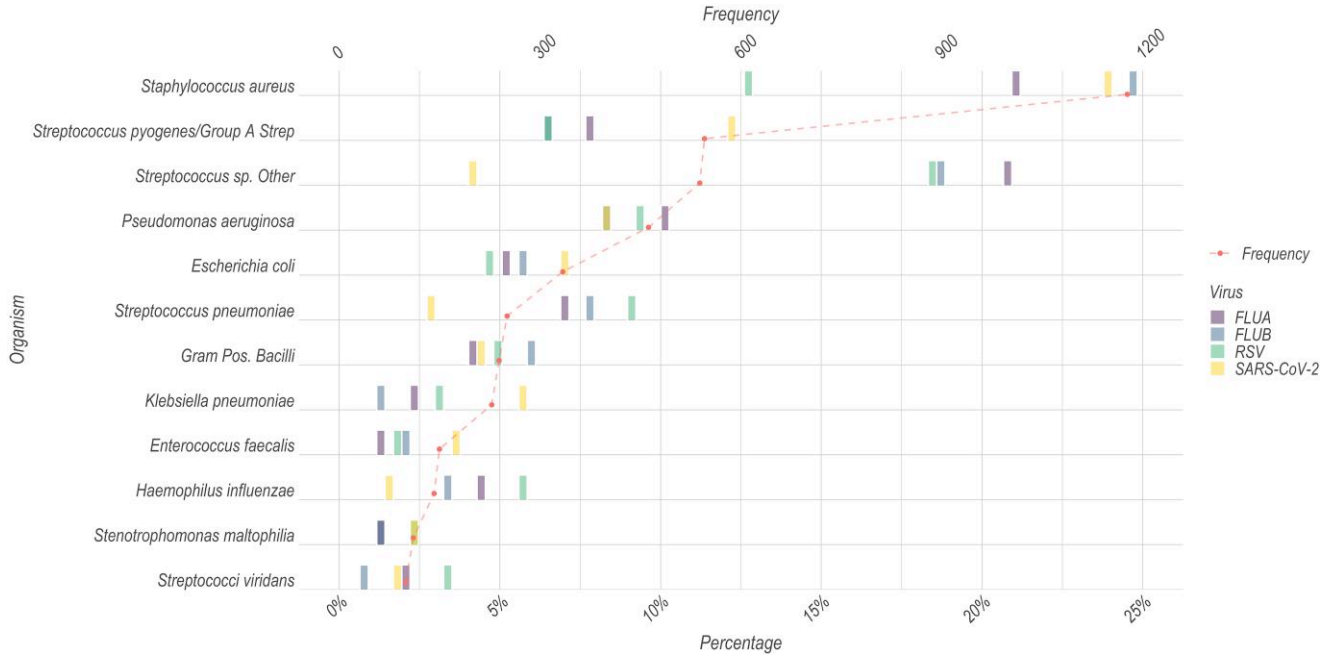

Figure 2. Distribution of organisms causing concurrent microbial infections among patients with respiratory viral infections. The red line indicates the overall frequency of individual organisms, while the colored bars specify the percentage of organisms among all those associated with each concomitant viral infection. Organisms depicted in the figure exhibit a minimum overall frequency >90. For values shown as a range, the median was used for visualization. Details have been listed in Supplementary Table 3. Abbreviations: FLUA, influenza A; FLUB, influenza B; RSV, respiratory syncytial virus.

(210/422, 49.8%), and RSV (219/428, 51.2%). Upper respiratory specimens with bacterial growth were collected from 969 cases (37.1%), lower respiratory specimens from 733 (28.1%), and unspecified from 947 (36.3%). Patients with SARS-CoV-2 had a greater percentage of bacterial infections diagnosed by lower respiratory specimen (n = 532, 35.4%) as compared with patients with FLUA (n = 104, 17.9%), FLUB (n = 44, 16.1%), and RSV (n = 53, 21.0%; Supplementary Table 2).

Most patients with SARS-CoV-2 and concomitant infection experienced a secondary infection (1584/2519, 62.9%), whereas

Table 3. Association of Viruses and Outcomes Among Patients With Concomitant Infection

Outcome: Effect	Odds Ratio Point Estimate (95% Wald Confidence Limits)	
	Unadjusted	Adjusted
Concomitant bacterial infection		
FLUA vs SARS-CoV-2	13.36 (12.35–14.45)	1.69 (1.48–1.93)
FLUB vs SARS-CoV-2	16.59 (14.93–18.43)	2.30 (1.97–2.69)
RSV vs SARS-CoV-2	11.54 (10.40–12.81)	1.56 (1.33–1.82)
Coinfection		
FLUA vs SARS-CoV-2	26.40 (23.92–29.15)	3.14 (2.61–3.77)
FLUB vs SARS-CoV-2	33.19 (29.26–37.64)	4.33 (3.54–5.30)
RSV vs SARS-CoV-2	23.53 (20.79–26.64)	2.55 (2.07–3.14)
Secondary infection		
FLUA vs SARS-CoV-2	4.91 (4.25–5.69)	0.62 (.50–.76)
FLUB vs SARS-CoV-2	5.79 (4.70–7.12)	0.76 (.58–.99)
RSV vs SARS-CoV-2	3.93 (3.19–4.84)	0.73 (.56–.95)
Concomitant bacterial–COVID-19 infection		
COVID-19 delta vs alpha	0.31 (.28–.35)	0.94 (.81–1.08)
COVID-19 wild type vs Alpha	0.86 (.78–.93)	0.61 (.54–.68)
Blood infection		
FLUA vs SARS-CoV-2	9.86 (8.67–11.22)	1.07 (.88–1.31)
FLUB vs SARS-CoV-2	13.10 (11.07–15.51)	1.51 (1.19–1.91)
RSV vs SARS-CoV-2	10.60 (9.06–12.41)	1.59 (1.27–2.00)
Respiratory infection		
FLUA vs SARS-CoV-2	14.96 (13.58–16.48)	2.49 (2.10–2.95)
FLUB vs SARS-CoV-2	17.69 (15.53–20.16)	3.24 (2.66–3.95)
RSV vs SARS-CoV-2	11.24 (9.83–12.86)	1.72 (1.40–2.11)
Staphylococcus aureus		
FLUA vs SARS-CoV-2	10.49 (9.01–12.22)	1.80 (1.38–2.34)
FLUB vs SARS-CoV-2	15.39 (12.72–18.63)	2.67 (1.99–3.60)
RSV vs SARS-CoV-2	5.83 (4.54–7.47)	1.54 (1.10–2.15)
Streptococcus pyogenes		
FLUA vs SARS-CoV-2	7.60 (5.98–9.67)	2.42 (1.68–3.50)
FLUB vs SARS-CoV-2	7.87 (5.51–11.23)	3.41 (2.18–5.35)
RSV vs SARS-CoV-2	5.80 (4.11–8.20)	1.32 (.83–2.11)
Pseudomonas aeruginosa		
FLUA vs SARS-CoV-2	14.75 (11.75–18.50)	0.89 (.62–1.29)
FLUB vs SARS-CoV-2	14.59 (10.49–20.28)	0.95 (.61–1.49)
RSV vs SARS-CoV-2	12.37 (9.14–16.75)	0.98 (.64–1.50)

Abbreviations: FLUA, influenza A; FLUB, influenza B; ICU, intensive care unit; RSV, respiratory syncytial virus.

a lower percentage of concomitant bacterial infections were categorized as secondary among individuals infected with FLUA (205/861, 23.8%), FLUB (96/422, 22.7%), and RSV (94/428, 22.0%; Table 2). The proportion of concomitant infections that involved bloodstream infection was slightly higher with SARS-CoV-2 (1145/2519, 45.5%) and RSV (182/428, 42.5%) than with FLUA (296/861, 34.4%) and FLUB (156/422, 37.0%).

The top 3 most common species were *S aureus* (n = 1177, 22.3%), *S pyogenes* (n = 546, 10.3%), and *P aeruginosa* (n = 462, 8.8%; Figure 2, Supplementary Table 3). *S aureus* was the most predominant species identified in patients for all viruses. *S pyogenes* was the second-most common species for SARS-CoV-2 and *P aeruginosa* for FLUA/B and RSV. The third-most common species was *P aeruginosa* for SARS-CoV-2, *S pyogenes* for FLUA, and *Streptococcus pneumoniae* for FLUB and RSV. When compared with SARS-CoV-2, FLUA and FLUB were associated with a higher risk of identifying *S aureus* and *S pyogenes* in concomitant infections. However, there was no significant difference in risks of identifying *P aeruginosa* between SARS-CoV-2 and other viruses (Supplementary Figure 1, Table 3).

When compared with SARS-CoV-2, the risk for concomitant bacterial infection was significantly higher for FLUA (unadjusted odds ratio [OR], 13.36; 95% CI, 12.35–14.45), FLUB (unadjusted OR, 16.59; 95% CI, 14.93–18.43), and RSV (unadjusted OR, 11.54; 95% CI, 10.40–12.81; Figure 3, Table 3). However, after adjusting for covariates, this association was substantially mitigated: FLUA (adjusted OR, 1.69; 95% CI, 1.48–1.93), FLUB (adjusted OR, 2.30; 95% CI, 1.97–2.69), and RSV (adjusted OR, 1.56; 95% CI, 1.33–1.82). The odds of coinfection remained elevated in the univariable and multivariable models. Yet, for secondary infection, adjustment for confounders reversed the association, and FLUA, FLUB, and RSV were associated with a lower odds of these delayed infections as compared with SARS-CoV-2. Supplementary Table 4 displays the risks for various outcomes across viruses stratified by hospitalization setting. The stratified analysis revealed that the higher risk of bacterial infection in patients with FLUA, FLUB, and RSV was driven largely by coinfection (Supplementary Table 5). While the adjusted odds of coinfection were higher in patients with FLUA (OR, 3.14; 95% CI, 2.61–3.77), FLUB (OR, 4.33; 95% CI, 3.54–5.30), and RSV (OR, 2.55; 95% CI, 2.07–3.14), they were lower for secondary infection when compared with SARS-CoV-2: FLUA (OR, 0.62; 95% CI, .50–.76), FLUB (OR, 0.76; 95% CI, .58–.99), and RSV (OR, 0.73; 95% CI, .56–.95; Figure 3, Table 3).

Subgroup analysis of COVID-19 waves (Supplementary Figure 2, Table 3) revealed lower odds of concomitant infection in COVID-19 for infections acquired during the initial wave (wild type predominant) and the delta-predominant wave as compared with the alpha-predominant wave. For blood and respiratory infections, the risk in SARS-CoV-2 was lower than in FLUB and RSV (Supplementary Figure 3).

DISCUSSION

Our cohort study of 885 004 viral infection cases reveals important differences in the odds of concomitant bacterial infections among common respiratory viruses. While SARS-CoV-2 is associated with overall lower odds of concomitant infections as compared with FLUA, FLUB, and RSV, this is driven by lower odds of coinfection (that occurring within 48 hours of viral infection). Yet, the odds of secondary infections (those occurring beyond 48 hours) were higher in patients with SARS-CoV-2.

These findings are consistent with systematic reviews performed earlier in the pandemic illustrating a relatively low

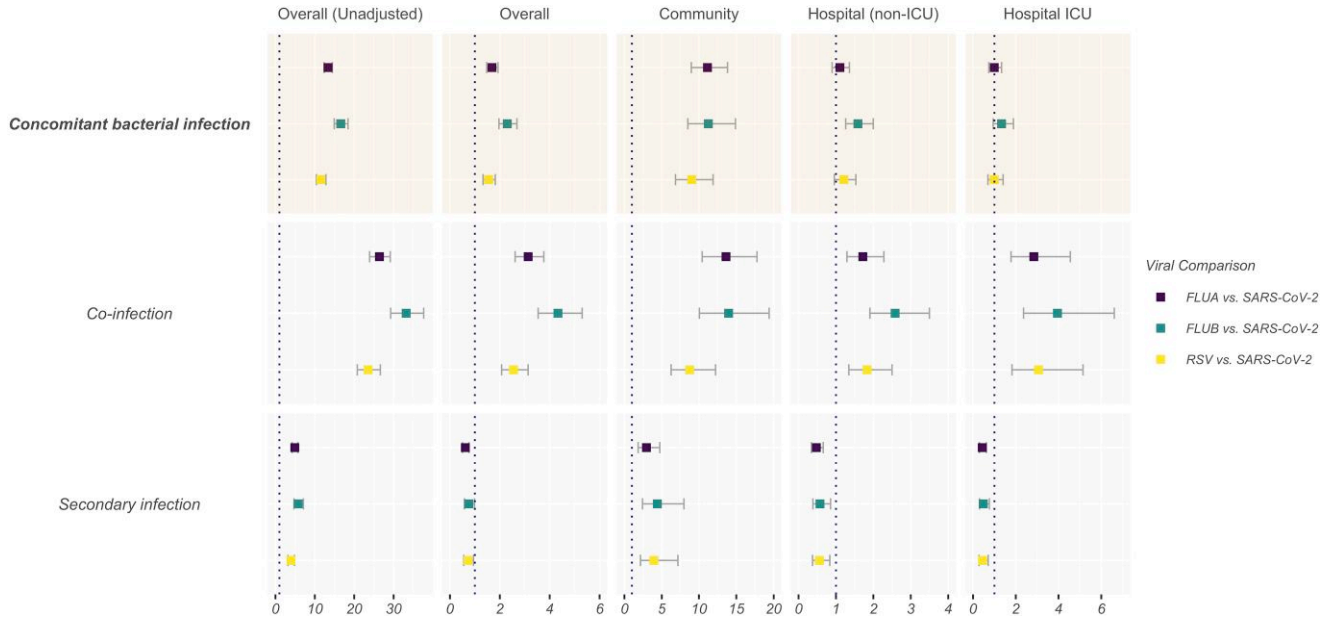

Figure 3. Association between viruses and various outcomes: overall and stratified by setting at the index date. Data are presented as adjusted odds ratios unless noted otherwise. Error bars indicate 95% CI. Viral cases were stratified into 4 groups based on patient setting at the time of the viral test: community, hospital (non-ICU), hospital ICU, and long-term care. Long-term care results are not displayed due to the detection of quasi-complete separation of data points. Abbreviations: FLUA, influenza A; FLUB, influenza B; ICU, intensive care unit; RSV, respiratory syncytial virus.

risk of concomitant infection in COVID-19 but a substantially elevated risk beyond 48 hours, particularly in those who are critically ill [4]. While the mechanisms are complex, respiratory infection with influenza and RSV is known to increase the risk of bacterial infections due to virus-induced inflammatory and immunologic effects, which may have a significant impact on morbidity and mortality [20, 21]. For example, bacterial coinfection/secondary infection may have contributed to >90% of fatalities in the 1918 influenza pandemic [22], roughly 75% of deaths in the 1957 flu pandemic [23], and more than half of deaths in the 2009 H1N1 pandemic [24]. While the mechanism of coinfection for COVID-19 is less clear, the potentially lower risk may be due to different pathologic effects, or it may reflect the lower risk of respiratory infection with other organisms due to containment measures early in the pandemic. A possible impact of containment measures on risk of concomitant bacterial infection within patients with SARS-CoV-2 is evident given the greater difference in odds of concomitant infection from different organisms. We observed a lower risk for concomitant infection caused by *S aureus* and *S pyogenes* among patients with COVID-19 as compared with those with influenza. Similarly, previous studies have also reported a decline in both infections during the early stage of the COVID-19 pandemic due to containment measures [25, 26]. Our analysis revealed a higher risk of infection with *P aeruginosa* among patients with COVID-19 as compared with patients with FLU. Similarly, a meta-analysis identified a significantly higher rate of *P aeruginosa* blood infection in COVID-19 as compared with non–COVID-19 [26]. Yet, the higher risk for hospital-associated and secondary infections in COVID-19 may reflect the burden of the pandemic and impact on testing practices (eg, blood culturing rates) [27]. Moreover, many patients with COVID-19 faced severe symptoms and developed nosocomial infections due to in-hospital medical intervention (eg, line infections, ventilator-associated pneumonia) [10, 28].

These findings have important implications to antimicrobial stewardship. Antimicrobial prescribing is common in patients with COVID-19, which can adversely affect antimicrobial resistance [12, 29, 30]. However, early empiric prescribing in patients who are not critically ill is not justified given the relatively low risk of coinfection. Such findings should be considered to support judicious prescribing decisions in patients with suspected or proven COVID-19.

While one of the main strengths of this study is its large size and population-based administrative data, there are some key limitations to mention. Since these databases do not provide patient symptomatology, we are unable to ascertain the difference between colonization and infection for respiratory tract bacterial infections. However, our findings are consistent whether the outcome is concomitant respiratory tract vs bloodstream infection, the latter of which is likely to be a true infection. Our data are limited by the different periods in which influenza and RSV were circulating, as compared with COVID-19. The years do not overlap, so there is a risk for confounding (ie, levels of bacterial

pathogens may be different among the viral groups). Especially during the COVID-19 years, lockdown procedures likely reduced the transmission of bacterial infections. In the future, researchers should consider repeating this study during periods when all viruses are cocirculating. Additionally, the frequency of testing will affect the odds of identifying a positive culture, which may have varied over the study period. Finally, since our population represents patients who were identified to have viral infections, differences in outcomes may reflect differences in testing practices among the viruses. Many patients who had less severe infections and/or were tested by other means (eg, rapid antigen testing) would not have been captured in our cohort. Yet, to alleviate the risk of selection bias associated with differences in testing, we adjusted for a number of covariates that may be associated with such testing practices (eg, age, health care setting, comorbidities) and conducted stratified analyses by setting. Given the substantial differences in point estimates before and after risk adjustment for covariates and for different settings, our study highlights the importance of risk adjustment when comparing risks for concomitant infections across different populations.

CONCLUSION

The overall prevalence of bacterial infections is comparable among FLUA, FLUB, and RSV but much lower for SARS-CoV-2. Among the concomitant infections, FLUA, FLUB, and RSV share similar rates of coinfection, which are higher than those of SARS-CoV-2; in contrast, SARS-CoV-2 demonstrates a higher risk of secondary infections than the others in the hospital and ICU settings. Targeted and ongoing surveillance could facilitate the identification of high-risk populations and the development of appropriate interventions to mitigate the impact of viral-related concomitant infections.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank IQVIA Solutions Canada Inc for use of its Drug Information File. Parts of this material are based on data and information compiled and provided by the Ontario Ministry of Health, OLIS, and Canadian Institute for Health Information.

Author contributions. Concept and design: Y. W., B. J. L., N. D., D. R. M., K. A. B. Analysis and interpretation of data: Y. W., B. J. L., N. D., D. R. M., K. A. B. Drafting of the manuscript: Y. W., B. J. L. Data acquisition: S. S. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Y. W. Administrative, technical, or material support: S. M. L.

Disclaimer. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Data sharing. The data set from this study is held securely in coded form at ICES. While legal data-sharing agreements between ICES and data providers prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS.

Financial support. This work was supported by a project grant from CIHR (grant 159503 to K. A. B. and N. D.); and by ICES, which is funded by an annual grant from the Ontario Ministry of Health and the Ministry of Long-term Care.

Potential conflicts of interest. All authors: No reported conflicts.

References

1. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect **2020**; 26:1622–9.
2. Meskill SD, O'Bryant SC. Respiratory virus co-infection in acute respiratory infections in children. Curr Infect Dis Rep **2020**; 22:3.
3. Martin-Loeches I, J Schultz M, Vincent JL, et al. Increased incidence of co-infection in critically ill patients with influenza. Intensive Care Med **2017**; 43:48–58.
4. Langford BJ, So M, Leung V, et al. Predictors and microbiology of respiratory and bloodstream bacterial infection in patients with COVID-19: living rapid review update and meta-regression. Clin Microbiol Infect **2022**; 28:491–501.
5. Weiser JN, Ferreira DM, Paton JC. Streptococcus pneumoniae: transmission, colonization and invasion. Nat Rev Microbiol **2018**; 16:355–67.
6. Oliva J, Terrier O. Viral and bacterial co-infections in the lungs: dangerous liaisons. Viruses **2021**; 13:1725.
7. McAuley JL, Hornung F, Boyd KL, et al. Expression of the 1918 influenza A virus PB1-F2 enhances the pathogenesis of viral and secondary bacterial pneumonia. Cell Host Microbe **2007**; 2:240–9.
8. Zamora-Cintas MI, López DJ, Blanco AC, et al. Coinfections among hospitalized patients with COVID-19 in the first pandemic wave. Diagn Microbiol Infect Dis **2021**; 101:115416.
9. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect **2020**; 81:266–75.
10. Hughes S, Troise O, Donaldson H, Mughal N, Moore LSP. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clin Microbiol Infect **2020**; 26:1395–9.
11. Patton MJ, Orihuela CJ, Harrod KS, et al. COVID-19 bacteremic co-infection is a major risk factor for mortality, ICU admission, and mechanical ventilation. Crit Care **2023**; 27:34.
12. Langford BJ, So M, Simeonova M, et al. Antimicrobial resistance in patients with COVID-19: a systematic review and meta-analysis. Lancet Microbe **2023**; 4:e179–91.
13. Russell CD, Fairfield CJ, Drake TM, et al. Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. Lancet Microbe **2021**; 2:e354–65.
14. Murray HC, Muleme M, Cooper D, et al. Prevalence, risk factors and outcomes of secondary infections among hospitalised patients with COVID-19 or post-COVID-19 conditions in Victoria, 2020-2023. Int J Infect Dis **2024**; 145: 107078.
15. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA **2009**; 302:1872–9.
16. Lin HC, Liu YC, Hsing TY, et al. RSV pneumonia with or without bacterial coinfection among healthy children. J Formos Med Assoc **2022**; 121:687–93.
17. Heikkinen T, Ruuskanen O. Upper respiratory tract infection. In: Laurent GJ, Shapiro SD, eds. Encyclopedia of respiratory medicine. Amsterdam: Elsevier, **2006**: 385–8.
18. Mondor L, Cohen D, Khan AI, Wodchis WP. Income inequalities in multimorbidity prevalence in Ontario, Canada: a decomposition analysis of linked survey and health administrative data. Int J Equity Health **2018**; 17:90.
19. Layton AT, Sadria M. Understanding the dynamics of SARS-CoV-2 variants of concern in Ontario, Canada: a modeling study. Sci Rep **2022**; 12:2114.
20. Pacheco GA, Gálvez NMS, Soto JA, Andrade CA, Kalergis AM. Bacterial and viral coinfections with the human respiratory syncytial virus. Microorganisms **2021**; 9: 1293.
21. Joseph C, Togawa Y, Shindo N. Bacterial and viral infections associated with influenza. Influenza Other Respir Viruses **2013**; 7:105–13.
22. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis **2008**; 198:962–70.
23. Hers JF, Masurel N, Mulder J. Bacteriology and histopathology of the respiratory tract and lungs in fatal Asian influenza. Lancet **1958**; 2:1141–3.
24. Gill JR, Sheng ZM, Ely SF, et al. Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. Arch Pathol Lab Med **2010**; 134:235–43.

25. McNeil JC, Flores AR, Kaplan SL, Hulten KG. The indirect impact of the SARS-CoV-2 pandemic on invasive group A *Streptococcus*, *Streptococcus pneumoniae* and *Staphylococcus aureus* infections in Houston area children. Pediatr Infect Dis J **2021**; 40:e313–6.
26. Marco DN, Canela J, Brey M, Soriano A, Pitart C, Herrera S. Assessing the influence of the COVID-19 pandemic on the incidence, clinical presentation, and clindamycin resistance rates of *Streptococcus pyogenes* infections. IJID Reg **2024**; 11: 100349.
27. Driedger M, Daneman N, Brown K, et al. The impact of the COVID-19 pandemic on blood culture practices and bloodstream infections. Microbiol Spectr **2023**; 11: e0263023.
28. Murthy S, Archambault PM, Atique A, et al. Characteristics and outcomes of patients with COVID-19 admitted to hospital and intensive care in the first phase of the pandemic in Canada: a national cohort study. CMAJ Open **2021**; 9:E181–8.
29. MacFadden DR, Maxwell C, Bowdish D, et al. Coronavirus disease 2019 vaccination is associated with reduced outpatient antibiotic prescribing in older adults with confirmed severe acute respiratory syndrome coronavirus 2: a population-wide cohort study. Clin Infect Dis **2023**; 77:362–70.
30. Langford BJ, So M, Raybardhan S, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clin Microbiol Infect **2021**; 27: 520–31.